ORIGINAL ARTICLE

Stage III Non–Small-Cell Lung Cancer

Population-Based Patterns of Treatment in British Columbia, Canada

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Introduction: Management of Stage III non–small-cell lung cancer (NSCLC) involves surgery, radiotherapy (RT), chemotherapy, and best supportive care. The aims were to describe the patterns of treatment in a population-based cohort of patients, and compare utilization of RT and chemotherapy to model estimates of need.

Methods: Patients diagnosed with Stage III NSCLC between January 1, 2000, to December 31, 2007, were identified from the British Columbia Cancer Agency database. Patients who had prior or concomitant malignancy were excluded. Patient demographics, tumor characteristics, and initial treatment were extracted. Survival data were derived from the British Columbia Vital Statistics Death Listings.

Results: 2365 patients with Stage III NSCLC were referred, of which 212 patients were excluded, leaving 2153 patients in the study population. Median age was 69 years. Disease stage was IIIA in 49% and IIIB in 51%. Histologies were squamous-cell carcinoma (31%), adenocarcinoma (27%), NSCLC not otherwise specified (31%), and other pathology (11%). Initial treatment included surgery in 12%, RT in 78%, and chemotherapy in 31%. Predicted RT utilization was 77% to 87% and chemotherapy 78%. From 2000 to 2007, curative-intent treatment increased from 21% to 35%, chemoradiotherapy from 8% to 18.6%, and concurrent chemoradiotherapy from 5.1% to 17.6%. Median survival was 30 months for patients who had curative surgery, 21 months for curative RT, 8 months for palliative treatment, and 5 months for best supportive care ($p < 0.001$).

Conclusion: RT utilization was similar to that predicted by models whereas chemotherapy utilization was less. During the study period, the proportion of patients receiving curative chemoradiotherapy doubled and of those receiving concurrent chemoradiotherapy trebled.

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Stage III non–small-cell lung cancer (NSCLC) as defined by Union for International Cancer Control TNM Classification 6th edition,[1] comprises a heterogeneous population of patients. The basis of staging can be either clinical or pathological following surgery. Disease extent varies from potentially curable small-volume locoregional disease to disease that is incurable because of its size, location, or pleural involvement. Management options range from any combination of surgery, radiotherapy (RT), and chemotherapy to best supportive care (BSC).

Evidence-based guidelines have been used to derive models of optimal utilization of RT and chemotherapy for patients with lung cancer.[2–5] These models use population characteristics, stage, and Eastern Cooperative Oncology Group (ECOG) performance status to determine whether patients would benefit from treatment. Estimates of optimal RT utilization at diagnosis in Stage III NSCLC range from 84% to 92%, and of chemotherapy is 88%.[2–4]

However, guideline-based treatments are not applicable to many patients with Stage III NSCLC.[6] Patients are typically elderly with comorbidities, a group poorly represented in clinical trials, which results in limited high-level evidence on which to base treatment for many patients.[7,8] Curative treatment usually requires multiple modalities,[9,10] which may be difficult to deliver in such patients.

In the general population of Stage III NSCLC patients, it is not clear what proportion is eligible for guideline-based treatment, in particular curative treatment. The aims of this study were to describe the patterns of treatment in a cohort of patients with Stage III NSCLC, define the proportion treated with curative intent, and compare the utilization of chemotherapy and RT to that predicted by published models.

MATERIALS AND METHODS

The British Columbia Cancer Agency (BCCA) is a provincial organization, with five regional cancer centers (four operating during the study era), which provides all RT, and manages the budget for all antineoplastic systemic therapy for

cancer patients diagnosed in British Columbia, Canada (population 4.5 million). Demographic data, tumor characteristics, treatment, and overall-survival outcome information for all patients with lung cancer referred to the BCCA for consultation are collected prospectively. Provincial management guidelines were available and regularly updated by the province-wide BCCA Lung Tumour Group comprising radiation oncologists, medical oncologists, respiratory physicians, and surgeons treating patients with lung cancers at the BCCA (http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Lung/start.htm). The BCCA also oversees the BC Cancer Registry, which houses demographic and pathologic information for all patients diagnosed with cancer in British Columbia.

All patients newly diagnosed with clinical or pathologic Stage III NSCLC between January 1, 2000 to December 31, 2007 were identified from this database. Patients had to have sufficient staging to determine the tumor, node, metastasis (TNM) stage. Stage groupings were based on the Union for International Cancer Control TNM Classification 6th edition.[1] Patients with a pathologically confirmed diagnosis (identified by ICD-0 histology codes 8000.3, 8010.3, 8012.3, 8013.3, 8014.3, 8020.3, 8021.3, 8046.3, 8070.3, 8071.3, 8072.3, 8073.3, 8074.3, 8130.2, 8083.3, 8140.3, 8250.3, 8252.3, 8253.3, 8255.3, 8260.3, 8480.3, 8481.3, 8490.3, 8550.3, and 8560.3) were included. Patients with concomitant malignancies diagnosed within 6 months of lung cancer diagnosis and those with a prior history of malignancy, other than non-melanomatous skin cancer and carcinoma-in-situ of the cervix, within 5 years preceding lung cancer diagnosis were excluded. Patients with a prior history of lung cancer or multifocal lung cancers were also excluded.

Details on patient demographics, tumor characteristics, and the first course of treatment (surgery, RT, chemotherapy, and BSC) were extracted. Initial treatment was coded as a variable within the BCCA database (as opposed to treatment for progression or recurrence). We also limited our definition of initial treatment to that which commenced within 6 months of diagnosis unless it was a planned course of sequential treatment modalities. For patients receiving RT as the primary treatment, we assumed curative intent if the minimum dose was 50 Gy. This dose was chosen to include patients who were treated with hypofractionated regimens such as 50 Gy in 20 fractions. For those receiving RT before or after surgery, coded as part of the initial treatment, this was assumed to be treatment with curative intent regardless of dose. Curative-intent chemotherapy was defined as that which was given immediately before or after surgical resection or immediately before or after, or concurrently with curative-dose RT. Treatment given for progressive or recurrent disease was not included. Survival data within the BCCA databases were derived from the British Columbia Vital Statistics Death Listings. All records were censored on June 30, 2010. Ethics approval was obtained from the BCCA Research Ethics Board.

Statistical analysis was performed using SPSS V18.[11] Comparisons were made using Pearson's χ^2 tests. Multivariable analysis was performed using Cox regression. Survival analysis was performed using Kaplan-Meier curves and comparisons were made using the log-rank test. A p value

of < 0.05 was interpreted as significant. The median follow-up of patients was 37 months, as calculated from the survival of patients alive at last follow-up.

RESULTS

Between January 1, 2000 and December 31, 2007, the British Columbia Cancer Registry identified 20,707 British Columbia residents with a new diagnosis of lung cancer. Of these, 13,131 (63%) were referred to BCCA for management and 2365 were patients with confirmed Stage III NSCLC. Two hundred and twelve patients were excluded because of concomitant malignancy ($n = 55$), prior history of malignancy ($n = 79$) or prior or synchronous lung cancer ($n = 78$). Two thousand one hundred and fifty-three patients formed the study population.

TABLE 1. Patient and Tumor Characteristics of the Study Cohort

	N	%
TOTAL	**2153**	**100**
Sex		
Male	1183	54.9
Female	970	45.1
Age (yrs)		
<50	145	6.7
50–64	647	30.1
65–79	1085	50.4
80+	276	12.8
ECOG PS		
ECOG 0–1	927	43.1
ECOG 2	442	20.5
ECOG 3–4	392	18.2
Unknown	392	18.2
Diagnosis period		
2000–2003	1015	47.1
2004–2007	1138	52.9
Stage		
Pathological IIIA[a]	160	7.4
Clinical IIIA	904	42.0
Pathological IIIB[a]	54	2.5
Clinical IIIB	1035	48.1
Laterality		
Right	1253	58.2
Left	887	41.2
Unknown[b]	13	0.6
Histology		
Squamous-cell carcinoma	661	30.7
Adenocarcinoma	589	27.4
Large-cell carcinoma	106	4.9
NSCLC NOS	668	31.0
NSCLC other	129	6.0

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, Non–small-cell lung cancer; NOS, not otherwise specified.
[a]Pathological staging refers to staging based on surgical resection.
[b]Tumors involving trachea.

Patient and tumor characteristics are shown in Table 1. The median age was 69 years (33–94). The majority of patients had good performance status (PS). Similar proportions had Stage IIIA and IIIB disease. We could not determine which patients with Stage IIIB cancers had pleural effusions, however, 59 (5%) underwent pleurodesis. The most common pathologies were NSCLC not otherwise specified and squamous-cell carcinoma. Eighteen percent of the patients had unknown ECOG PS. These patients were similar to those with known ECOG PS except for 17% aged 80 years or older compared to 12% of those with known ECOG PS (*p* = 0.005).

There were no significant differences in the population distribution according to sex, age, ECOG PS, and stage over the 8 years of the study. There were some differences in pathological classification over time. From 2000 to 2007, the proportion of squamous-cell carcinoma decreased from 30% to 24%, adenocarcinoma from 35% to 24%, and large-cell carcinoma from 14% to 3% (*p* < 0.0001). Conversely, NSCLC not otherwise specified increased from 1% in 2000 to 47% in 2007.

Surgery

Two hundred and fifty patients (12%) received surgery as part of their initial treatment. Of these, 96 (39%) had surgery alone, 36 (14%) had neoadjuvant treatment before surgery, and 118 (47%) had surgery and adjuvant therapy (Table 2). Lobectomy was the most frequent operation performed (*n* = 153.61%), followed by pneumonectomy (*n* = 81.33%), and segmental resection (*n* = 16.6%).

Radiotherapy

RT was part of initial treatment in 1681 patients (78%). (Table 2) Curative RT was only given to 16.9% of the patients.

Of the 363 patients who received curative RT, the median dose was 60 Gy (*n* = 173, 47.6%). Doses higher than 60 Gy (*n* = 108, 29.8%) were occasionally used, most commonly 66 Gy (*n* = 46, 12.7%). These doses were usually delivered in 2 Gy fractions. Other common fractionation schemes were 55 Gy in 20 fractions (*n* = 20, 5.5%) and 50 Gy in 20 fractions (*n* = 15, 4.1%).

Palliative RT alone was the most common overall treatment in this cohort (*n* = 1228, 57%). The median RT dose was 20 Gy in five fractions (*n* = 526, 42.8%). Other common doses were 30 Gy in 10 fractions (*n* = 257, 20.9%), 8 or 10 Gy in 1 fraction (*n* = 84, 6.8%), and 40 Gy in 15 fractions (*n* = 35, 2.9%). Five patients received endobronchial brachytherapy alone as palliative treatment.

The use of preoperative and postoperative RT was uncommon (*n* = 90, 4.2%). The most frequent doses were 50 Gy in 20 to 25 fractions (*n* = 31, 34.4%) and 45 Gy in 20 to 25 fractions (*n* = 27, 30%).

Chemotherapy

Six hundred and sixty-eight patients (31%) received chemotherapy as part of their initial treatment (Table 2). Similar proportions received palliative chemotherapy (*n* = 279, 12.9%) and chemotherapy combined with curative RT (*n* = 287, 13.3%). The most common palliative chemotherapy regimens were cisplatin and etoposide (*n* = 91, 32.6%), cisplatin and vinorelbine (*n* = 87 31.2%) and cisplatin and gemcitabine (*n* = 30, 10.8%). A cisplatin–etoposide combination was used in 237 patients (82.6%) treated with curative RT. Preoperative and postoperative chemotherapy was infrequently used (*n* = 102, 4.7%). Cisplatin–etoposide (*n* = 45) and cisplatin–vinorelbine (*n* = 40) were the most frequent regimens in this setting.

TABLE 2.　Initial Treatment of Study Cohort – n (% of Stage)

Treatment	Stage IIIA *n* = 1064	Stage IIIB *n* = 1089	Total *n* = 2153
Surgery alone	62 (5.8)	34 (3.1)	96 (4.5)
Surgery + adjuvant chemotherapy	49 (4.6)	12 (1.1)	61 (2.8)
Surgery + adjuvant radiotherapy	43 (4.1)	8 (0.7)	51 (2.3)
Surgery + adjuvant chemotherapy and radiotherapy	6 (0.6)	0 (0)	6 (0.3)
Neoadjuvant chemotherapy + surgery	1 (0.1)	2 (0.2)	3 (0.1)
Neoadjuvant radiotherapy + surgery	1 (0.1)	0 (0)	1 (0)
Neoadjuvant chemotherapy + radiotherapy + surgery	22 (2.1)	8 (0.7)	30 (1.4)
Neoadjuvant radiotherapy + surgery + adjuvant chemotherapy	1 (0.1)	0 (0)	1 (0)
Neoadjuvant chemotherapy + surgery + adjuvant radiotherapy	1 (0.1)	0 (0)	1 (0)
TOTAL CURATIVE SURGERY	186 (17.5)	64 (5.9)	250 (11.6)
Curative radiotherapy + concurrent chemotherapy	161 (15.1)	104 (9.5)	265 (12.3)
Neoadjuvant chemotherapy + curative radiotherapy	15 (1.4)	7 (0.6)	22 (1)
Curative radiotherapy alone	43 (4.0)	33 (3.0)	76 (3.5)
TOTAL CURATIVE RADIOTHERAPY	219 (20.5)	144 (13.2)	363 (16.9)
Palliative radiotherapy + palliative chemotherapy	69 (6.5)	124 (11.4)	193 (9)
Palliative radiotherapy alone	471 (44.3)	564 (51.7)	1035 (48)
Palliative chemotherapy alone	17 (1.6)	69 (6.4)	86 (4)
TOTAL PALLIATIVE TREATMENT	557 (52.4)	757 (69.6)	1314 (61.0)
No active treatment	102 (9.6)	124 (11.4)	226 (10.5)
TOTAL BEST SUPPORTIVE CARE	102 (9.6)	124 (11.4)	226 (10.5)

TABLE 3. Distribution of Prognostic Factors Among Initial Treatment Groups *n* (% of Variable)

	Curative Surgery *n* = 250	Curative Radiotherapy *n* = 363	Palliative Treatment *n* = 1314	BSC *n* = 226	*p*
Age					
Median in yrs (range)	65 (37–84)	63 (40–92)	71 (33–94)	75 (36–92)	<0.001
Stage					
IIIA	186 (17.5)	219 (20.6)	557 (52.3)	102 (9.6)	<0.001
IIIB	64 (5.9)	144 (13.2)	757 (69.5)	124 (11.4)	
Pathology					
SCC	65 (9.8)	121 (18.3)	415 (62.8)	60 (9.1)	<0.001
Adenocarcinoma	126 (21.4)	96 (16.3)	305 (51.8)	62 (10.5)	
LCC	12 (11.3)	10 (9.4)	68 (64.2)	16 (15.1)	
Other	47 (5.9)	136 (17.1)	526 (66)	88 (11)	
ECOG PS					
0–2	176 (12.9)	305 (22.3)	754 (55.1)	134 (9.8)	<0.001
3–4	17 (4.3)	10 (2.6)	306 (78.1)	59 (15.1)	
Unknown	57 (14.5)	48 (12.2)	254 (64.8)	33 (8.4)	
Period of diagnosis					
2000–2003	106 (10.4)	133 (13.1)	669 (65.9)	107 (10.5)	<0.001
2004–2007	144 (12.7)	230 (20.2)	645 (56.7)	119 (10.5)	

BSC, best supportive care; SCC, squamous-cell carcinoma; LCC, large-cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment Combinations

Treatment was divided into four groups for further analysis (Table 3). The median age of patients undergoing curative treatment was significantly lower than of those treated palliatively. As would be expected, curative treatment was more commonly given to patients with Stage IIIA disease and those of good PS. However, even in patients who were ECOG zero to two, only 35.2% received curative treatment. There were some differences in the treatment of different pathological subtypes with a greater proportion of patients with adenocarcinoma undergoing surgery. The use of curative RT increased significantly in the second half of the study period with a corresponding reduction in palliative treatment.

Figure 1 shows changes in treatment over time. The use of curative treatment increased over time from 21.1% in 2000 to 35% in 2007. This was largely because of the increased utilization of curative chemoradiotherapy, which increased from 8% in 2000 to 18.6% in 2007. The use of neoadjuvant chemotherapy before RT decreased from 2.9% to 1% and the use of concurrent chemoradiotherapy increased from 5.1% to 17.6% over the same time period. Use of curative RT alone showed minimal change from 2.9% in 2000 to 3.9% in 2007. The use of palliative chemotherapy either alone or with palliative RT decreased from 16.7% in 2000 to 10.6% in 2007. The proportions receiving surgery and BSC remained similar over the years.

In patients with Stage IIIA NSCLC, the use of curative surgery increased from 14.7% to 18.3% and that of curative chemoradiotherapy from 11.6% to 25.5% from 2000 to 2007. For patients with Stage IIIB NSCLC the use of surgery was similar over the years, being 6.2% in 2000 and 7% in 2007

whereas curative chemoradiotherapy increased from 4.8% to 12% over this time period.

Comparison With Models of Evidence-Based Utilization

The distribution of stage and PS was inserted into the RT models published by Delaney et al.[2] and Tyldesley et al.[3] to estimate the optimal (initial) utilization of RT in this cohort. If there were factors influencing the recommendation for RT that were not documented in this cohort (such as presence of symptoms, positive margins, and patient preferences), then these proportions were taken directly from the model (Fig. 2).
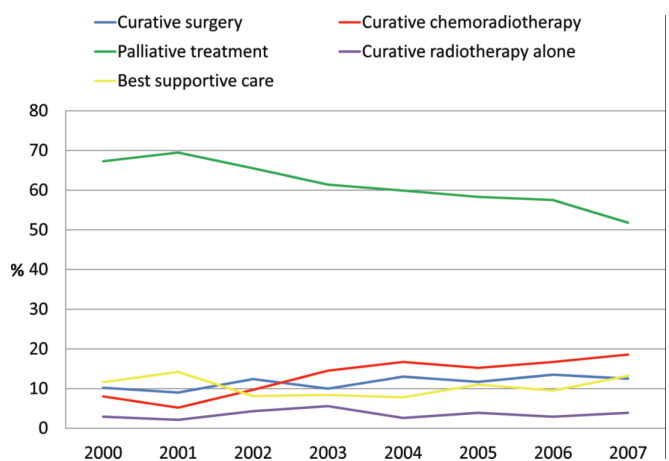
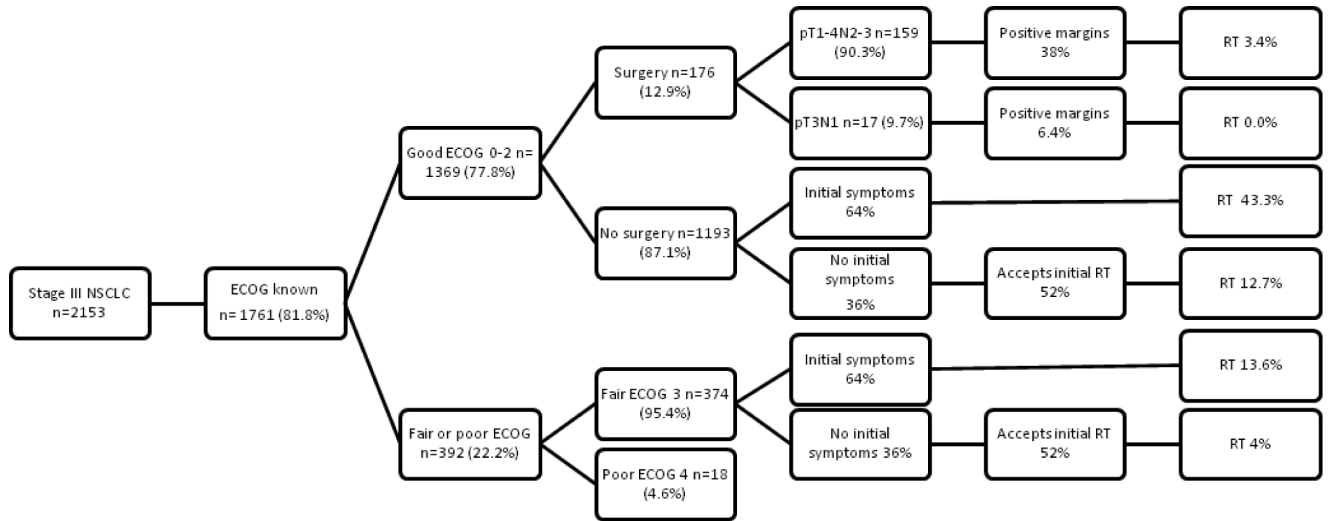**FIGURE 1.** Treatment groups for study cohort by year of diagnosis.

FIGURE 2.   Study population applied to radiotherapy utilization model published by Tyldesley et al.[3]

The optimal utilization of RT was predicted to be 77% and 87% on the basis of Tyldesley's model and Delaney's model, respectively. The actual RT utilization of 78% is similar to the former estimate. The main difference between the models is that Tyldesley accounts for Stage III patients who have a preference for BSC over RT whereas Delaney's model presumes that all patients who have an indication for RT choose to receive it.

For chemotherapy, the population characteristics were entered into a chemotherapy model published by Jacob et al.[4] (Fig. 3). From this, the optimal utilization of chemotherapy at diagnosis was predicted to be 77.7%. The chemotherapy utilization of 31% in this study is well less than this. This model, however, assumes that all patients were fit enough to receive chemotherapy, and does not take patient preferences into account.

Logistic regression analysis was performed to investigate factors that predicted for the use of chemotherapy. Patients with adenocarcinoma histology (hazard ratio [HR] = 1.50, 95% confidence interval [CI] 1.13–2.00, p = 0.005), and those diagnosed from 2004 onward (HR 2.36, 95% CI 1.90–2.96, $p < 0.0001$) were more likely to receive chemotherapy. Increasing age was associated with less frequent use of chemotherapy with patients (50–64 years HR = 0.66; 65–79 years HR = 0.15; ≥ 80 years HR = 0.10 relative to <50-year olds) as was poor PS (HR = 0.11, 95% CI 0.07–0.17, $p < 0.0001$).

Overall Survival

The median overall survival for all patients was 11 months (95% CI 10.4–11.6 months). The 1-year and 5-year survivals were 47% and 9%, respectively. As 94% of deaths were from lung cancer, lung cancer specific survival was not separately analyzed. Median survival was significantly better for women than for men (Table 4). Survival decreased with increasing age and poorer PS. Median survival, 1-year survival and 2-year survival were 10 months, 42% and 21% in 2000, respectively, and increased to 12 months, 51% and 27% in 2007, respectively. However, this change in survival over time was not statistically significant. For patients with Stage IIIA NSCLC median survival increased from 13 months in 2000 to 15 months in 2007 ($p = 0.06$), and for
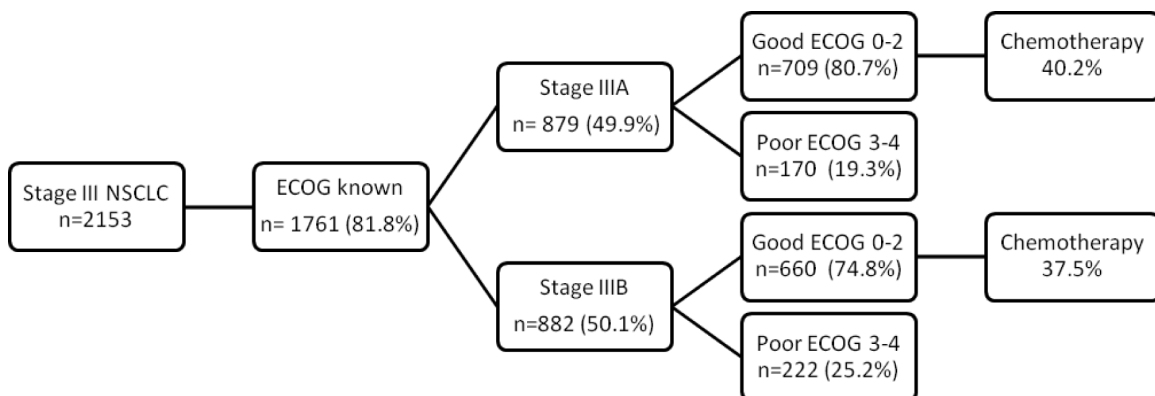

FIGURE 3.   Study population applied to chemotherapy utilization model published by Jacob et al.[4]

those with Stage IIIB NSCLC from 7 months to 9 months (p = not significant).

Patients who had surgery combined with other therapies had a median survival of 34 months (95% CI 27.5–40.5 months), curative surgery alone 27 months (95% CI 19.6–34.3 months), curative RT and chemotherapy 24 months (95% CI 20.6–27.4 months), and curative RT alone 13 months (95% CI 8.3–17.7 months). Palliative treatment resulted in a median survival of 8 months (95% CI 7.5–8.5 months) and BSC 5 months (95% CI 3.9–6.1 months) ($p < 0.001$).

On multivariable analysis, factors predictive of improved survival were female sex, younger age, better PS, Stage IIIA disease, and later period of diagnosis (Table 5). Pathology was not an independent predictor of survival.

DISCUSSION

Stage III NSCLC is a diverse disease that can be challenging to treat because the population it occurs in is elderly, often with associated smoking-related comorbidities.

TABLE 4. Univariable Overall-Survival Estimates for Study Cohort

	n	Median Survival in Months (95% CI)	3 Year Survival (%±SE)	P
Sex				
Male	1183	9 (8.3–9.7)	11.6 ± 1.0	
Female	970	12 (11.1–12.9)	17.8 ± 1.3	<0.001
Age (yrs)				
<50	145	15 (11.6–18.4)	21.8 ± 3.6	
50–64	647	13 (11.8–14.2)	17.9 ± 1.6	
65–79	1085	10 (9.2–10.8)	13.4 ± 1.1	
≥80	276	7 (5.8–8.2)	6.3 ± 1.5	<0.001
ECOG PS				
0–2	1369	13 (12.2–13.8)	18.1 ± 1.1	
3–4	392	4 (3.4–4.6)	1.9 ± 0.7	
Unknown	392	9 (7.7–10.3)	13.7 ± 1.8	<0.001
Year				
2000	275	10 (8.5–11.5)	12.6 ± 2.1	
2001	233	8 (6.7–9.3)	10.3 ± 2.1	
2002	258	10 (8.3–11.6)	15.5 ± 2.3	
2003	249	11 (9.1–12.9)	15.0 ± 2.3	
2004	269	11 (9.3–12.7)	13.7 ± 2.2	
2005	283	11 (9.5–12.5)	15.9 ± 2.2	
2006	275	11 (9.3–12.7)	16.2 ± 2.4	
2007	311	12 (10.3–13.7)	14.7 ± 2.2	NS
Stage				
IIIA	1064	13 (12.1–13.9)	18.9 ± 1.3	
IIIB	1089	8 (7.3–8.7)	10.4 ± 1.0	<0.001
Pathology				
Squamous	661	10 (9.0–11.0)	12.5 ± 1.3	
Adenocarcinoma	589	13 (11.8–14.1)	19.2 ± 1.7	
Large-cell	106	9 (7.2–10.8)	15.3 ± 3.6	
NSCLC other	797	10 (9.1–10.9)	12.2 ± 1.2	<0.001

SE, standard error; ECOG PS, Eastern Cooperative Oncology Group performance status; NS, not significant; NSCLC, non–small cell lung cancer.

TABLE 5. Multivariable Analysis of Factors Predictive of Survival

Variable	Odds Ratio[a]	95% CI	P
Sex			
Male	1		0.03
Female	0.73	0.56–0.97	
Age (yrs)			
<50	1		<0.0001
50–64	1.39	0.86–2.25	
65–79	2.01	1.30–3.32	
80+	4.50	2.45–9.00	
ECOG PS			
0–2	1		<0.0001
3–4	4.47	2.45–8.14	
Unknown	0.97	0.68–1.38	
Stage			
IIIA	1		<0.0001
IIIB	1.93	1.46–2.56	
Year diagnosed			
2000–2003	1		
2004–2007	0.45	0.34–0.61	<0.0001

ECOG PS, Eastern Cooperative Oncology Group performance status; CI, confidence interval.

[a]Odds ratio > 1 predicts for higher risk of death.

Although there are many trials of treatment in NSCLC, these are often limited to younger, fitter patients, and the applicability of results to the general lung cancer population is poorly studied. To gain a better understanding of treatment patterns at a population level, we retrospectively reviewed the management of patients with confirmed Stage III NSCLC. This cohort of patients was mainly staged without positron emission tomography (PET) scans. PET scanning only became available in British Columbia in 2005 and was limited to one center with limited capacity, so would only have been performed in a minority of patients in the study population.

This cohort was similar to other Western lung cancer populations in terms of age and PS.[12–15] The proportion of women was similar to other North American populations but more than that described in Australia, New Zealand, Scotland, and the Netherlands.[6,12–14] Pathology distribution showed that 31% of the patients were diagnosed with NSCLC without any further pathological subtyping. This proportion increased significantly from 1% in 2000 to 47% in 2007. It is possible that there was a change in the method of tissue collection with greater reliance on fine needle aspiration biopsy and interventional radiologist biopsies in the latter years. Information on the nature of biopsies taken was not collected. Nevertheless, this group of unspecified NSCLC is greater than that described in the United States.[13] During the study era, pathological subtyping was not a determinant of treatment. However, it is now well recognized that different pathological subtypes are associated with differential response rates to systemic therapies.[16] The International Association for the Study of Lung Cancer now has a detailed classification of adenocarcinoma, which includes molecular subtyping.[17] These recommendations

need to be implemented to direct appropriate selection of therapies for patients.

In this contemporary population of patients with Stage III NSCLC, the most common treatment was RT alone, given in just over half of all patients. This is greater than in the American and Australian populations (Table 6).[12,13] The use of surgery or surgery combinations was similar to that documented in Australia but less than that in the United States. Chemotherapy as a single modality was used less frequently. In combination with RT, it was used more often than in Australia but less than in the United States. However, patients in the current study were the most likely to receive some form of active treatment for their lung cancer, with only 10.5% receiving BSC alone compared to 18.5% in the United States and 28% in Australia.

A selection bias in patients referred to BCCA may account for some of the differences regarding surgery and BSC. During the study period, 63% of all patients diagnosed with lung cancer were referred to BCCA. The true proportion receiving either BSC or surgery alone would have been higher if all diagnoses of lung cancer in the province were included. A previous study in British Columbia has shown that in 2002, the crude referral rate of lung cancer patients to BCCA within 6 months of diagnosis was 67%.[18] In this study, surveys were sent to family physicians enquiring about stage and PS. The nonreferred group was characterized by two groups of patients, those with localized disease and good PS who received surgery, and those with metastatic disease and poor PS who received BSC. Only 28% of the nonreferred patients had Stage III NSCLC, therefore, of all lung cancer patients, an additional 10% of Stage III cases may have been excluded from our analysis. Given that all RT in the province is delivered at BCCA centers, none of these patients would have received initial RT, although they may have been treated with surgery or chemotherapy in the community.

Differences in population characteristics may partly explain the differences in patterns of treatment. Eighty percent of the Australian population and 72% of the American population had a comorbidity, which may have influenced treatment. This variable was not recorded in the current population although there is no reason to think this would be dissimilar across Western populations.

The main difference between the Canadian and other populations was the less frequent use of chemotherapy. Meta-analyses published in 1995 and updated in 2002 showed that the addition of chemotherapy to RT or to BSC resulted in improved survival.[19,20] Surveillance, Epidemiology and End Results data from 2001 show that 58.4% of patients with Stage III NSCLC received chemotherapy as part of initial treatment.[13] This comprised 11.5% receiving chemotherapy alone, 26.2% with RT, and 10.7% with surgery. The BCCA guidelines of 2000 recommended chemoradiotherapy for nonsurgical patients with good PS and minimal weight loss. Although the overall use of chemotherapy was lower than that in other populations, the majority of patients (79%) receiving curative RT also received chemotherapy, greater than the proportion (60%) described in a U.S. pattern of care study.[21] During the period of the study, the proportion receiving chemoradiotherapy doubled, and that receiving concurrent chemoradiotherapy trebled.

The BCCA guidelines also recommended palliative chemotherapy over BSC in patients of good PS not suitable for curative treatment. However, the incorporation of palliative chemotherapy for Stage III NSCLC in British Columbia has been less than in other jurisdictions. Patient comorbidities may have precluded treatment although we would expect this to be similar across affluent Western populations. Patient preferences may have been a factor. In metastatic lung cancer, only 22% of patients would have chemotherapy for a survival benefit of 3 months although 68% would choose it for symptom relief without any survival benefit.[22] In addition, palliative RT provides symptomatic relief for chest symptoms without the systemic toxicity of chemotherapy.[23] Pragmatic clinicians may be less likely to incorporate treatment associated with a modest survival benefit into clinical practice.

A lack of access to medical oncologists may also have resulted in the lower chemotherapy use. We do not have data regarding the proportion of the study population who saw a medical oncologist. A review of SEER data showed that 36% of patients who did not receive chemotherapy for their advanced lung cancer were not seen by a medical oncologist.[24] During the study period, there were unfilled medical oncology positions in British Columbia. Although this may have created delay in access to a medical oncologist, it is unlikely to have served as an absolute barrier for referral. At all BCCA centers, the medical and radiation oncologists work closely together, and patients are triaged to see either or both subspecialties at the time of initial referral by a triaging physician, who may be a clinician from either specialty.

In this population-based cohort, 38% of patients with Stage IIIA NSCLC, 22.7% of patients with Stage IIIB NSCLC, and 28.5% overall received treatment with curative intent. With the staging system in use during the period of the study, patients with malignant pleural effusion would have been included in the Stage IIIB group, although they were not candidates for curative treatment. The new staging system, TNM 7th edition now classes these patients as having Stage IVa disease as their prognosis is worse than that of patients having Stage IIIB disease on the basis of T4 or N3 characteristics.[25] Other population-based studies have also documented a low proportion of patients suitable for treatment with curative

TABLE 6. Comparison with Other Population-Based Studies of Utilization of Different Treatments in Stage III NSCLC (%)

	USA 2001[13] n = 11,263	New South Wales, Australia 2001–2002[12] n = 308	British Columbia, Canada 2000–2007 N = 2153
Surgery alone	6.6	4	4.5
Radiotherapy alone	16.5	31	51.5
Chemotherapy alone	11.5	11	4
Surgery combination	10.7	7	7.1
Radiotherapy and chemotherapy	36.2	19	22.4
Best supportive care	18.5	28	10.5

NSCLC, non–small-cell lung cancer.

intent. In New Zealand in 2004, Stevens et al.[14] found that 11.5% of Stage III patients received curative treatment. In Australia from 2001 to 2002, 26% of Stage III patients received a combination treatment with two or three treatment modalities in 2001 to 2002, presumably treated with curative intent, although this does not include patients who may have received curative RT alone.[12]

RT with curative intent was only given in 16.9% of all patients or 19.1% of all nonsurgical patients. The respective figures for chemotherapy combined with RT were 13.3% and 15.1%. De Ruysscher et al.[6] calculated that 41% of inoperable Stage III patients in the Netherlands would be eligible for concurrent chemoradiotherapy on the basis of age or comorbidity. In a study of 276 consecutive Dutch patients treated between 2004 and 2005, Ouwens et al.[26] found that 39% of Stage III patients were treated with chemoradiotherapy. These figures are more than double of that seen in the current population, suggesting that patient and clinician factors may be responsible.

The characteristics of patients enrolled in clinical trials often do not reflect those of the general lung cancer population, who tend to be older, with comorbidities and a range of PS. Thus, selecting patients for combined treatment can be difficult as results often have to be extrapolated to a patient who would be ineligible for trial entry. Large tumor volume and compromised respiratory function are also factors that have to be taken into consideration but are poorly reported in clinical trials. Tumor volume alone, however, does not necessarily contraindicate a radical RT approach.[27]

Clinician factors may also explain the differences in treatment. The difference in the use of chemoradiotherapy between the Dutch and Canadian populations may be because of different attitudes of oncologists in British Columbia. However, attitudes are changing. A survey of Canadian radiation oncologists in 2010 found that 61% of respondents would recommend radical chemoradiotherapy for a patient with a bulky Stage IIIB lung cancer compared to only 31% in survey from 1993.[28] Clinicians who see a smaller volume of lung cancer patients (<10 per year) are also less likely to recommend chemoradiotherapy for unresectable Stage III NSCLC.[29]

The utilization of RT was similar to that predicted by models of optimal utilization, showing that British Columbian residents who were referred to BCCA were likely to receive RT as indicated. Even if we adjust our RT utilization estimate to account for the potential additional 10% of non-referred Stage III cases, the overall RT utilization rate in the province remains high at 71%, comparable to model estimates. However, chemotherapy utilization was appreciably lower than that predicted. It is possible that the model overestimates the optimal utilization of chemotherapy as factors that influence the decision for chemotherapy, such as patient comorbidities and preference, are not taken into account. Nevertheless, this population was less likely to receive chemotherapy than contemporary populations in the United States, Australia, and the Netherlands.[12,13,26]

The treatment patterns over time show increasing use of curative therapies particularly radical RT combined with chemotherapy. The main increase was seen from 2001 to 2003, which predated the availability of PET scanning from 2005 onward. Use of PET scans to stage patients could potentially lead to stage migration with improved survival as a result of better patient selection rather than treatment. There was a gradual increase in survival throughout the whole study period rather than after 2005 alone, suggesting a treatment effect. However, this modest 2-month improvement in survival did not reach statistical significance.

The survival seen in this population according to treatment modality is comparable to, if not better than, randomized trials reported in the literature.[30] The median survival of 34 months for patients receiving surgery combination treatment is greater than the 16 months reported in the European Organisation for Research and Treatment of Cancer study[9] and the 24 months reported in an Intergroup study.[10] Similarly, patients receiving curative chemoradiotherapy had a superior survival of 24 months compared to the 18 months and 22 months seen in the EORTC and Intergroup studies, respectively.[9,10] These results support the opinion that definitive thoracic irradiation delivered concurrently with chemotherapy is a model of curative treatment for Stage III NSCLC, which has not been seriously challenged.

This study reports on patterns of care for patients with Stage III NSCLC treated in a contemporary time period. The management of lung cancer continues to evolve, and the applicability of the results to current practice need to be interpreted in light of the new lung cancer staging system adopted in 2010 and the use of fluorodeoxyglucose-PET scans to routinely stage patients. The main impact of the new staging system for the study cohort would be to upstage those with malignant pleural effusions to Stage IVA disease. We know that at least 5% of patients with Stage IIIB NSCLC in this study would fall into this category, but this can be as high as 33% evaluated from an audit of 105 patients with Stage IIIB NSCLC seen in south-west Sydney, Australia over the same time period as this study (unpublished data, S. Vinod, January 2011). Similarly, the increased sensitivity of staging with FDG-PET would upstage some of these patients to Stage IV disease, and potentially downstage a few as well. The effect of both these factors is likely to increase the rate of utilization of curative treatment and improve outcomes of the study cohort by excluding incurable patients. The comparisons made were with other similar studies that used the same staging system mostly in the pre-PET era. The adoption of evidence-based practice from clinical trials at the population level is not often reported. This study shows a shift in patterns of care over time resulting in increased use of curative treatment, particularly chemoradiotherapy, which translated into modest improvement in survival, although this did not reach statistical significance.

CONCLUSION

To the best of our knowledge, this is the largest report on the outcomes of a population-based cohort with Stage III NSCLC. Almost a third of patients had no pathological subtyping of their cancer, a process that is becoming increasingly important in the era of targeted therapies and recognized differing efficacy of systemic agents according to pathology. There was an increase in the use of curative treatment over time, which may account for the modest improvement seen

in survival. The use of RT was in keeping with the estimates from published models. However, the use of chemotherapy remains lower than that in other contemporary populations. Further increases in the proportion receiving curative RT can be facilitated by the technological advances in RT, which allow better target definition and reduced treatment toxicity. Improvements in supportive care may also allow more patients to receive combined modality treatment. Patients with Stage III NSCLC account for up to a third of the NSCLC population, and improving the use of curative treatment in this group is likely to impact overall survival for the whole population.

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